

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 April 1997 (09.04.97)	
International application No. PCT/CA96/00585	Applicant's or agent's file reference 7479-21 JHW
International filing date (day/month/year) 30 August 1996 (30.08.96)	Priority date (day/month/year) 01 September 1995 (01.09.95)
Applicant PUGH, Sydney, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
24 March 1997 (24.03.97)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Céline Faust Telephone No.: (41-22) 730.91.11
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PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C04B 35/447, A61L 27/00, C04B 41/87		A1	(11) International Publication Number: WO 97/09286
			(43) International Publication Date: 13 March 1997 (13.03.97)
(21) International Application Number: PCT/CA96/00585 (22) International Filing Date: 30 August 1996 (30.08.96) (30) Priority Data: 60/003,157 1 September 1995 (01.09.95) US 08/576,238 21 December 1995 (21.12.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/576,238 (CIP) Filed on 21 December 1995 (21.12.95) (71) Applicant (for all designated States except US): MILLENIUM BIOLOGIX, INC. [CA/CA]; Suite 200, 785 Midpark Drive, Kingston, Ontario K7M 7G3 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): PUGH, Sydney, M. [CA/CA]; 499 Maple Lawn Drive, Glenburnie, Ontario K0H 1S0 (CA). SMITH, Timothy, J., N. [CA/CA]; 21 Pickwick Place, Kingston, Ontario K7M 1M1 (CA). SAYER, Michael [CA/CA]; 97 Younge Street, Kingston, Ontario K7M 1E4 (CA). LANGSTAFF, Sarah, Dortha [CA/CA]; 35 Nelson Street, Kingston, Ontario K7L 3W6 (CA).			(74) Agent: WOODLEY, John, H.; Sim & McBurney, 6th floor, 330 University Avenue, Toronto, Ontario M5G 1R7 (CA). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: AN ARTIFICIAL STABILIZED COMPOSITION OF CALCIUM PHOSPHATE PHASES PARTICULARLY ADAPTED FOR SUPPORTING BONE CELL ACTIVITY			
(57) Abstract <p>This invention relates to a bioactive artificial sintered composition for providing a morphology capable of consistently supporting bone cell activity thereon. The composition comprises stabilized calcium phosphate phases developed by the conversion of a hydroxyapatite substance in the presence of stabilizing entities at sintering temperatures into insolubilized and stabilized tricalcium phosphate. The present invention has numerous applications in medical diagnostics for the assessment of abnormal bone cell activity as well as for medical therapeutics, including bone and dental tissue replacement and repair as well as for <i>ex vivo</i> bone graft tissue engineering.</p>			

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 96/00585

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-35 Bioactive artificial composition comprising stabilized calcium phosphate phases including insoluble and stabilized Ca (PO₄)
2. Claims 36 Method for the ex vivo engineering of mineralized collagenous matrix comprising four steps.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-35

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 7479-21JHW	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 96/ 00585	International filing date (day/month/year) 30/08/1996	(Earliest) Priority Date (day/month/year) 01/09/1995
Applicant MILLENIUM BIOLOGIX, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.
☐ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☒ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the **title**, ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 - Figure No. ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 96/00585

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-35 Bioactive artificial composition comprising stabilized calcium phosphate phases including insoluble and stabilized Ca (P04)
2. Claims 36 Method for the ex vivo engineering of mineralized collagenous matrix comprising four steps.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-35

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 96/00585

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C04B35/447 A61L27/00 C04B41/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C04B A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 26872 (MILLENIUM BIOLOGIX INC.) 24 November 1994 cited in the application see the whole document ---	1-35
A	DATABASE WPI Week 8923, Derwent Publications Ltd., London, GB; AN 89-169871 & JP,A,1 111 763 (JGC CORP.) 28 April 1989 see abstract --- -/--	1-35

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

21 November 1996

Date of mailing of the international search report

19.02.97

Name and mailing address of the ISA

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Authorized officer

LUETHE H.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/ISA 96/00585

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 8446, Derwent Publications Ltd., London, GB; AN 84-284542 & JP,A,59 174 567 (AGENCY OF IND. SCI. TECH.) 3 October 1984 see abstract ---	1-35
A	ANATOMY AND EMBRYOLOGY, vol.170, no.3, December 1984 pages 247-247 - 256, XP002019145 S.J. JONES ET AL. cited in the application see the whole document -----	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 96/00585

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9426872	24-11-94	AU-A- 6791994	12-12-94
		CA-A- 2152477	24-11-94
		EP-A- 0666902	16-08-95
		FI-A- 953186	24-07-95
		NO-A- 952811	14-07-95

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 12 DEC 1997
WIPO PCT

Applicant's or agent's file reference 7479-21JHW	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)	
International application No. PCT/CA96/00585	International filing date (day/month/year) 30/08/1996	Priority date (day/month/year) 01/09/1995
International Patent Classification (IPC) or national classification and IPC C04B35/447		
Applicant MILLENIUM BIOLOGIX, INC. et al.		



1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 24/03/1997	Date of completion of this report 10. 12. 97
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Mini, A Telephone No. (+49-89) 2399-8560 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA96/00585

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-33 as originally filed

Claims, No.:

1-37 as received on 21/08/1997 with letter of 19/08/1997

Drawings, sheets:

1-14 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA96/00585

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
 - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 37.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 37.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA96/00585

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims..
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

cf Separate Sheet, Item III

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1 - 36.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1, 3, 5-10, 12-20, 22-26, 30-32
	No: Claims 2, 4, 11, 21, 27-29, 33-36
Inventive step (IS)	Yes: Claims
	No: Claims 1 - 36
Industrial applicability (IA)	Yes: Claims 1 - 36
	No: Claims

2. Citations and explanations

cf. Separate Sheet, Item II

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA96/00585

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

2. Non-written disclosures (Rule 70.9)

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

cf. Separate Sheet, Item I

ITEM I

1. It is maintained that the term "**stabilizing entities**" used in Claims 1 and 13 is vague and indefinite and, as such, renders the scope of these claims unclear. This in particular since the alleged invention is based on the presence of such "entities" (cf. the application page 5, line 19-page 6, line 2); thus the relevant claims should contain a clear definition of such "entities". Accordingly, the claim should be amended to remove this defect by introducing in said claims the features of Claims 5 and 17 respectively (Article 6 PCT).

Consequently it is also maintained that the term "**entities**" itself is not clear and should be replaced by a more appropriate one (e.g. molecule(s), atom(s), compound(s) or oxide(s)) (cf. Claims 5,6-10, 13,15-20 and 26).

2. It is no longer maintained that a sintering temperature being comprised between 900°C and 1100°C is a feature essential to the performance of the invention.
3. Claim 23 would be allowable with a revised (see. point 1 above) independent claim 13.
4. It is maintained that claims "shall not rely, in respect of the technical features of the invention, on references to the description or drawings" Rule 6.2(a) PCT. The request of the applicant of introducing such a reference in present Claim 25 cannot therefore be allowed.

ITEM II

1. Reference is made to the following documents:

D1 =DATABASE WPI, Week 8923, AN 89-169871 & JP,A,1111763

D2 = WO,A,9426872

2. Additionally to the comments made under ITEM I above applicant's attention is

drawn to the fact that the purposive statement "for providing a morphology capable of consistently support bone cell activity thereon" cannot be considered as describing a technical feature apt for distinguishing the subject-matter of Claim 1 from tricalcium phosphate based sintered composition of the prior art. In fact the product of D1 is suitable for use as a material for artificial bones or teeth and as such is considered to be a "bioactive" composition in the meaning of present Claim 1. Furthermore the indication that the morphology of the composition of D1 is defined as "capable of consistently support bone cell activity thereon" does not give any information on the morphology itself.

3. It is maintained that the subject-matter of **Claims 1,3,5,7,13-15,17,19 and 30-32** is anticipated by document D1.
- 3.1 Present Claim 1 is concerned with a bioactive artificial sintered composition comprising stabilized calcium phosphate phases which can be produced (cf. Claim 13) by converting a hydroxyapatite substance into primarily alpha tricalcium phosphate by sintering in the presence of "stabilizing entities" (selected from silicon, aluminium, zirconium, titanium, boron, germanium, chromium, vanadium, niobium and mixtures thereof).
- 3.2 Document D1 discloses a "bioactive" sintered composition based on the conversion product of hydroxyapatite into tricalcium phosphate in the presence of a compound or mixture of compounds of Ti, Zr, Al. D1 does not explicitly say that said compound(s) act as a stabilizer. This however appears to be implicitly disclosed in D1 in which the bioactive compact is produced by the same method as in the present application (mixing hydroxyapatite and a stabilizers and converting the hydroxyapatite at sintering temperatures). The fact that D1 does not contain any teaching or any indication about any superior biological performance beyond strength and toughness is not relevant for the assessment of novelty since the compounds used in the process of D1 are the same of the "entities" used in the present application.
4. It is maintained that the subject-matter of **Claims 4,11,21,27-29 and 33-36** does not involve an inventive step in the light of the disclosure of D1 combined with that

of document D2 which discloses a calcium phosphate thin film on which bone cells can be cultured to permit evaluation of bone cell functional properties (cf. D2 Claims 1,3,5,8 and 9).

ITEM III

1. The subject-matter of present Claim 37 does not have a single special feature in common with the subject-matter of present claims 1-36, and hence is the subject-matter of Claim 37 is not so linked with the subject-matter of Claims 1-36 as to form a single general inventive concept. The method of Claim 37 refers to "an artificial stabilized composition" in general and, since it does not disclose the compound(s) forming a said composition, a variety of compounds other than "insolubilized and stabilized tricalcium phosphate" are embraced by its subject matter.
2. Similarly, the only common technical feature between Claim 24 and the other claims is the presence of polycrystalline sintered stabilized calcium phosphate phases which are anticipated by D1. Hence, the subject-matter of Claim 24 is not so linked with the subject-matter of Claims 1-23 and 25-36 as to form a single general inventive concept. In order to overcome this objection Claim 24 should be amended by specifying that the calcium phosphates phases have been stabilized by the method of Claim 13 by means of the stabilizers disclosed in claims 5 and/or 17 (essential features).

Claims

1. A bioactive artificial sintered composition for providing a morphology capable of consistently supporting bone cell activity thereon, said composition comprising stabilized calcium phosphate phases developed by the conversion of a hydroxyapatite substance in the presence of stabilizing entities at sintering temperatures into insolubilized and stabilized tricalcium phosphate.
2. A composition as claimed in claim 1, wherein said stabilized tricalcium phosphate is primarily alpha tricalcium phosphate.
3. A composition as claimed in claim 2, wherein said composition is in the form of a powder, film, thick coating or a three-dimensional bulk material.
4. A composition as claimed in claim 3, wherein said film has a thickness of about 0.1 μm to 10 μm .
5. A composition as claimed in claim 3, wherein said hydroxyapatite substance before sintering is provided on a substrate comprising a component selected from the group consisting of silicon entities, aluminum entities, zirconium entities, barium entities, titanium entities and mixtures thereof.
6. A composition as claimed in claim 5, wherein said stabilizing entities are released from said substrate during sintering or added in solution to the hydroxyapatite substance before sintering.
7. A composition as claimed in claim 3, 5, or 6, wherein said stabilizing entities are selected from the group consisting of silicon, germanium, chromium, vanadium, niobium, titanium, boron, aluminum, zirconium and mixtures thereof.

8. A composition as claimed in claim 2, wherein said composition is coated onto a quartz substrate, silicon entities being released from the quartz upon sintering, into the forming calcium phosphate phases to stabilize the alpha tricalcium phosphate.

9. A composition as claimed in claim 3, wherein said silicon entities are added in solution to the hydroxyapatite substance before sintering.

10. A composition as claimed in claim 1 or claim 9, wherein said silicon entities are tetrapropyl orthosilicate.

11. A composition as claimed in claim 1, wherein said calcium phosphate phases are in a ratio of 50:50 to 20:80 for hydroxyapatite to alpha tricalcium phosphate.

12. A composition as claimed in claim 1, wherein said composition is insoluble in physiological fluids of pH of approximately 6.4 to 7.3.

13. A process for stabilizing an artificial sintered composition of calcium phosphate phases having a morphology suitable for supporting bone cell activity thereon, said process comprising converting a hydroxyapatite substance, into primarily alpha tricalcium phosphate by sintering, and providing stabilizing entities which stabilize and insolubilize the formed alpha tricalcium phosphate within the phosphate phases.

14. A process as claimed in claim 13, wherein the composition formed is a powder, film, coating or a three-dimensional solid.

15. A process as claimed in claim 14, wherein said hydroxyapatite substance is applied onto a substrate comprising a component selected from the group consisting of silicon entities, aluminum entities, zirconium entities, titanium entities, boron entities, germanium

entities, chromium entities, vanadium entities, niobium entities and mixtures thereof.

16. A process as claimed in claim 15, wherein said stabilizing entities are released from said substrate into the hydroxyapatite phases developed during sintering.

17. A process as claimed in claim 14 or 16, wherein said stabilizing entities are selected from the group consisting of silicon, aluminum, zirconium, titanium, boron, germanium, chromium, vanadium, niobium and mixtures thereof.

18. A process as claimed in claim 17, wherein said hydroxyapatite substance is applied to a quartz substrate, silicon entities being released from the quartz upon sintering, into the forming calcium phosphate phases to stabilize the alpha tricalcium phosphate.

19. A process as claimed in claim 13, wherein silicon entities are added in solution to the hydroxyapatite substance before sintering.

20. A process as claimed in claim 13 or 19, wherein said silicon entities are tetrapropyl orthosilicate.

21. A process as claimed in claim 13, wherein said calcium phosphate phases are in a ratio of 50:50 to 20:80 for the ratio of hydroxyapatite to alpha tricalcium phosphate.

22. A process as claimed in claim 13, wherein sintering of the hydroxyapatite substance is done at temperatures of about 900°C to 1100°C.

23. A sintered artificial microporous polycrystalline structure for supporting bone cell activity, said structure being made by the process of claim 13.

24. A sintered artificial microporous polycrystalline structure for supporting bone

cell activity, said structure comprising sintered stabilized calcium phosphate phases having a globular surface morphology of loosely interconnected rounded granules with interconnected micropores in said structure.

25. A polycrystalline structure of claim 24, wherein said structure has said globular surface morphology of Figure 10.

26. A polycrystalline structure of claim 25, wherein said rounded granules have a lateral dimension in the range of 0.5 to 1 μm .

27. An implantable calcified bone matrix comprising:

- a) a structure for supporting said matrix;
- b) a layer of stabilized calcium phosphate phases developed by the conversion of a hydroxyapatite substance in the presence of stabilizing entities at sintering temperatures into tricalcium phosphate where said stabilizing entities insolubilize and stabilize the calcium phosphate phases;
- c) a boundary layer deposited by osteoblasts cultured on said layer of stabilized calcium phosphate phases; and
- d) a mineralizing collagenous matrix secreted by such cultured osteoblasts.

28. An implantable calcified bone matrix of claim 27, wherein said matrix is free of bone cells including osteoblasts.

29. An implantable calcified bone matrix of claim 27, wherein said matrix includes a patients bone cells including osteoblasts.

30. An implantable calcified bone matrix of claim 27, wherein said matrix is capable of being resorbed by osteoclasts.

AMENDED SHEET

31. A bulk ceramic microporous structure made with the composition of claim 1 or 2.

32. A bulk ceramic microporous structure as claimed in claim 31, wherein said structure has an internal macroporosity.

33. An implantable device coated with the sintered composition of claim 1 or 2.

34. An implantable device consisting essentially of the composition of claim 1.

35. A method for the culturing of functional bone cells, said method comprising
- applying a suspension of bone cells in physiological media to an artificial sintered film of stabilized calcium phosphate phases on a substrate comprising stabilized and insolubilized alpha tricalcium phosphate complexes.

36. A kit for monitoring and quantifying the activity of bone cells, said kit comprising;
- a substrate having a sintered film of calcium phosphate phases containing stabilized and insolubilized alpha tricalcium phosphate,
- a multiwell bone cell culture device adhered to said substrate.

37. A method for the *ex vivo* engineering of mineralized collagenous matrix, the method comprising the steps of:
- providing an artificial stabilized composition having a globular surface morphology of loosely interconnected rounded granules with interconnected micropores,
- applying a suspension of osteoblasts in physiological media on the composition,
- incubating the mineralized collagenous bone matrix selected by the osteoblasts from the culture; and

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- implanting the isolated collagenous bone matrix in a patient.

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